Principles of Clinical Pharmacology,
NIH, April 24, 2003

Role of FDA in Guiding Drug Development

Carl Peck

Center for Drug Development Science

Georgetown University

Washington DC

?

Why **FDA ?**

When **does FDA get involved ?**

How **does FDA guide drug development?**

What **comprises FDA guidance ?**

New ! **What's new at FDA ?** New !

Guiding Drug Development

Why FDA?

- **FD&C Act: history and its supporters**
  - **resulted from public safety events or public health challenges**
    - **~ 1900, 1938, 1960, 1972, 1987**
  - **a uniquely American phenomenon**
- **Evolution of Drug Regulation (R. Temple)**

SAFETY → EFFECTIVENESS → INDIVIDUALIZATION

….. → PERSONALIZATION

When

does FDA get involved ?

- Preclinical (voluntary) phase
  - animal testing
  - subpart E, Fast Track, Orphan designations
- Clinical development phase
  - IND
- NDA review
- Marketing phase
  - ADR surveillance
  - new uses, product changes

How does FDA guide drug development?

- Written guidances
  - Regulations, guidelines (incl. ICH), guidances[1]
  - Regulatory letters
  - (Statute, Congressional Reports)
- Face-to-face meetings
- FDA Advisory Committee meetings
- Podium presentations

1 Website - www.fda.gov

What comprises FDA guidance ?

- Standards
  - chemistry and manufacturing controls (CMC)
  - preclinical animal toxicology requirements
  - ethics of human clinical trials
  - documentary requirements for INDs, & NDAs
  - Electronic records (21 CFR part 11)
- Clinical trials
  - safety
  - effectiveness
  - trial design

FDA *Today*: Increasing Transparency

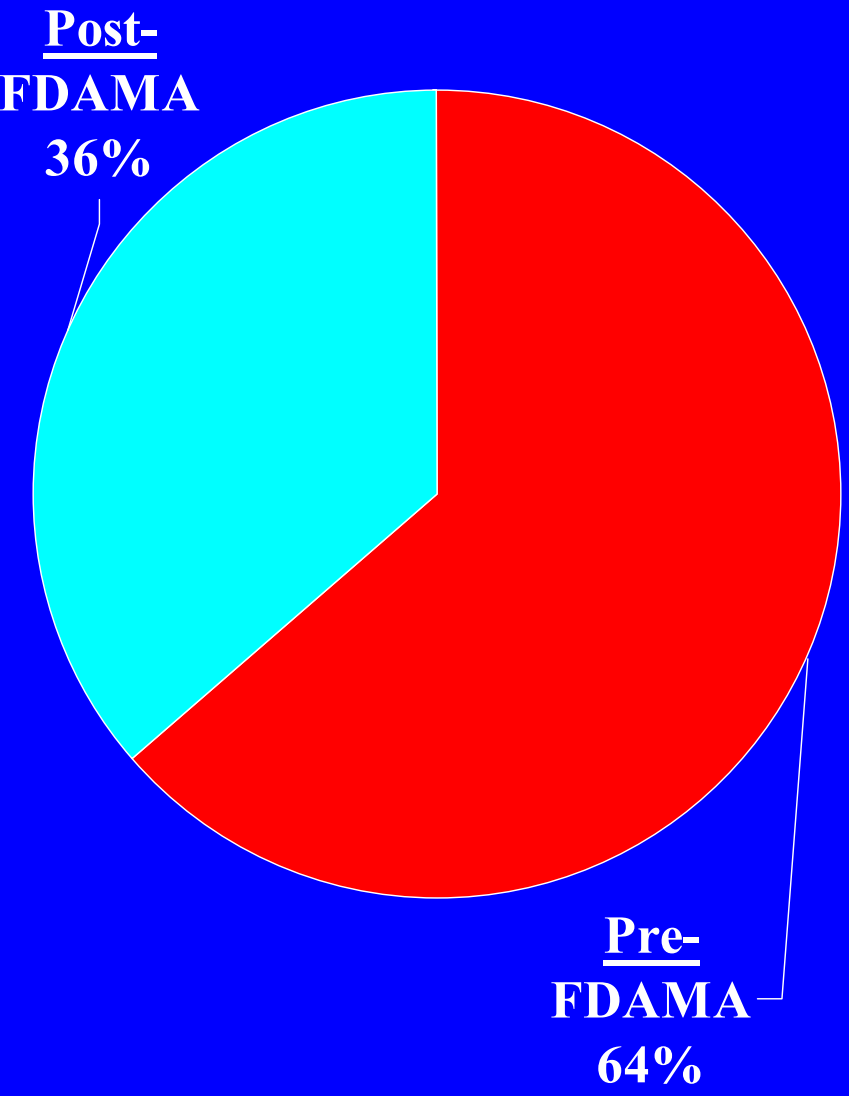
- **GUIDANCES** (http://www.fda.gov/cder/guidance.htm)
  - *344* guidances (final/draft, FDA/ICH), 3/31/00
- **Guidance documents:**
  - *Cannot legally bind FDA or the public*
  - *Recognizes value of consistency & predictability*
  - *Because a company wants assurance*
  - *So staff will apply statute & regulations consistently*

Center For Drug Evaluation and Research List of Guidance Documents

Monday, March 25, 2002

"Guidance documents represent the Agency's current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both."

FDA *Today*: Increasing Transparency



Pre-FDAMA

- 228 guidances
- 243 month period

= 11.1 guidances/year

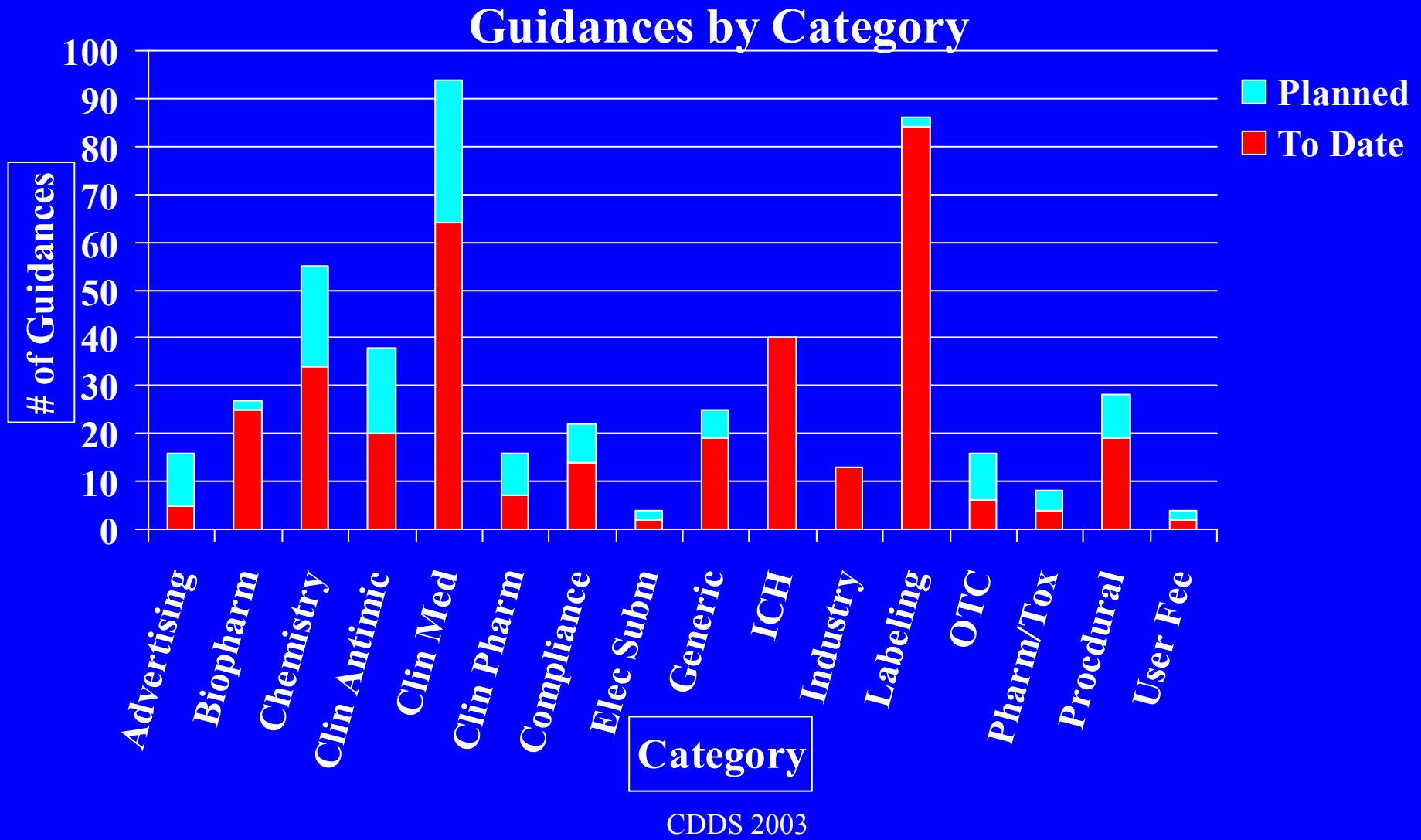
Post-FDAMA

- 130 guidances
- 28 month period

★ **= 55.7 guidances/year** ★

CDDS 2003

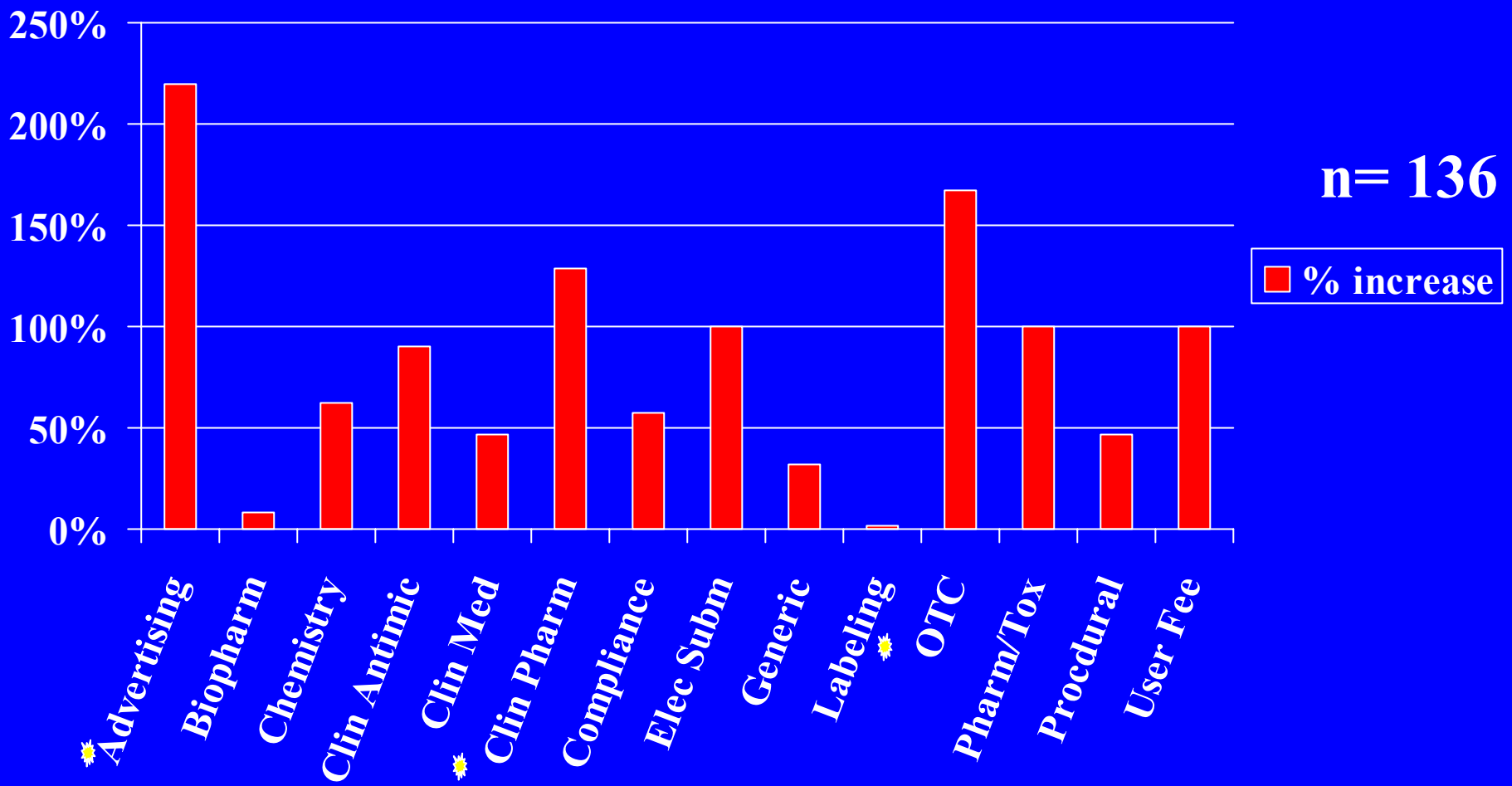
FDA *Tomorrow*: Planned Guidances



CDDS 2003

FDA *Tomorrow*: Guidance Topics

Planned % Increase of Guidances by Category



CDDS 2003

www.fda.gov/cder/guidance/guidance-agenda.htm

EXAMPLE 1
Clinical/Pharmacological Guidances*

1. **Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies *In Vitro*** (97); ***In Vivo*** (99)
2. **Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application** (98)
3. **Pharmacokinetics in Patients with Impaired Renal Function** (98)
4. **Population Pharmacokinetics** (99)
5. **Exposure-Response** (02)

* Website - www.fda.gov

EXAMPLE 2
Clinical/Pharmacological Guidances*

1. General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products
2. Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

* Website - www.fda.gov

EXAMPLE 3
Clinical/Medical Guidances[1]

- ***Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*** (98)
- **Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs** (93)
- **Study of Drugs ... used in the Elderly** (89)
- **Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research (draft 3/00)**

* 41 final, 12 draft guidances Website - www.fda.gov

New Formulations and Doses of Already Approved Drugs*

- Where ***blood levels ... are not very different***, it may be possible to conclude ... is effective on the basis of **pharmacokinetic data** ***alone***.

- Even ***if blood levels are quite different***, if there is **a well-understood relationship between blood concentration and response**, ..., it may be possible to conclude ... is effective on the basis of **pharmacokinetic data** ***without*** an additional clinical efficacy trial.

*** Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products", May 1998**

EXAMPLE 4
Biopharmaceutics Guidances*

- **Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design** (92)

- **Trazodone Hydrochloride (tablets) In Vivo Bioequivalence and In Vitro Dissolution Testing** (88)

* Website - www.fda.gov

EXAMPLE 5
FDA Modernization Act of 1997
"FDAMA"

- Sec. 111. ***Pediatric*** studies of drugs
  - **PK bridging studies**

- Sec. 115. Clinical investigations
  - **support of *one* adequate and well-controlled clinical investigation by *"confirmatory evidence"* comprising PK or PK/PD**

FDAMA, Sec. 111
Pediatric studies of drugs

"(g) Definitions. - the term `pediatric studies' or `studies' means at least one clinical investigation (that .. may include *pharmacokinetic* studies) in pediatric age groups...."

Pediatric Labeling Regulations
(21 CFR 201.56)

"FDA may approve a drug for pediatric use based on ... studies in adults, with other information supporting pediatric use…. additional information supporting pediatric use must ordinarily include data on the *pharmacokinetics* of the drug in the pediatric population ….Other information, such as data on ***pharmacodynamic*** **studies**…."

FDAMA, Sec. 115

Clinical investigations

"If the Secretary determines, based on relevant science, that data from *one* adequate and well-controlled clinical investigation and *confirmatory evidence* …. are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence.."

FDAMA, Sec. 115
Clinical investigations

CONGRESSIONAL COMMITTEE REPORTS[1]

- *"confirmatory evidence"* = "scientifically sound data from any investigation in the NDA that provides substantiation as to the safety and effectiveness of the new drug"
- confirmatory evidence = "consisting of earlier clinical trials, *pharmacokinetic* data, or other appropriate scientific studies"

1 House Commerce Committee, 10/7/97, and Committee of Conference on Disagreeing votes of the two Houses, 11/9/97

FDA – what's new?

- New Leadership
  - Commissioner (McClellan)
  - Deputy Comm. (Crawford)
  - Principle Assoc. Comm. (Lumpkin)
  - Chief Counsel (Troy)
  - CBER Director (Goodman)
- Initiatives (pro-business)
  - Improving drug development, manufacturing, 21CFRprt11
- CBER → CDER: protein therapeutics

FDA Alumni Assn. Lunch
March 3, 2003

McClellan Initiative: FDA leadership to improve drug development

- Aims to achieve predictable, 1-cycle NDA/BLA reviews
  - 'Root cause' analysis
  - Guidance to industry
    - Intensified FDA-industry communications
  - Continuous marketing application project
  - Reviewers and Reviews
    - Training
    - Review standards
    - Peer review
    - 'Quality Systems' review improvements

“Academics” Meeting
April 5, 2003

How can academics help?

- Academics can (and have) investigate 'root causes' of inefficient contemporary drug development practices
- Can share findings and innovative solutions with FDA, such as
  - Causes and remedies for failed phase 3 trials
  - Rationale and examples to motivate abandonment of inefficient, costly, empirical traditional drug development, to be
  - Replace empiricism with a quantitative, causal-model and simulation approach, that
  - Fits well with facilitated FDA approval pathways, such as
    - "Single Trial" Approval (FADAMA sec. 115a)
    - 5/98 Effectiveness Guidance
    - Dose-response, Exposure-Response, Population PK guidances, and many others

How can academics help?

- Academics can contribute advanced methods for optimization of clinical drug testing, including
  - Learn-confirm approach
  - Integration of intensified early clinical pharmacology
  - Pharmacometrics, including
    - population PK/PD
    - modeling & simulation of clinical trials
  - Pharmacogenetic guided development
  - Effective use of biomarkers and Surrogate Endpoints
  - Maximal utilization of all effectiveness & safety information derived during development

Reference Materials

1. Report of a Workshop on Confirmatory Evidence to Support a Single Clinical Trials as a Basis for New Drug Approval. Peck & Wechsler: Drug Inf J 36 (3):517-534, 2002
2. Hypothesis: A Single Clinical Trial plus Causal Evidence of Effectiveness is Sufficient for Drug Approval - Peck, Sheiner, & Rubin, in press, Clin Pharm Ther 2003
3. "Simulation of Clinical Trials". In Annual Rev Pharmacol Toxicol. Holford, Monteleone, Kimko, Peck : Vol. 40, 209-234, 2000.
   - 11th EUFEPS Conference on Optimising Drug Development – Integrating New Concepts and Tools. Co-organised with the ECPM European Center of Pharmaceutical Medicine Workshop Series on Frontiers in Drug Development, Basel Congress Center, December 8–10, 2003
4. Workshop Announcements:
   - Clinical Development of Oncologic Agents: Challenging the Tradition April 23-24, 2003 GUMC, Washington, DC (CDDS)
   - Tools for Pre-Approval Drug Safety Evaluation April 29, 2003 - May 27, 2003 (Academics to CDER)

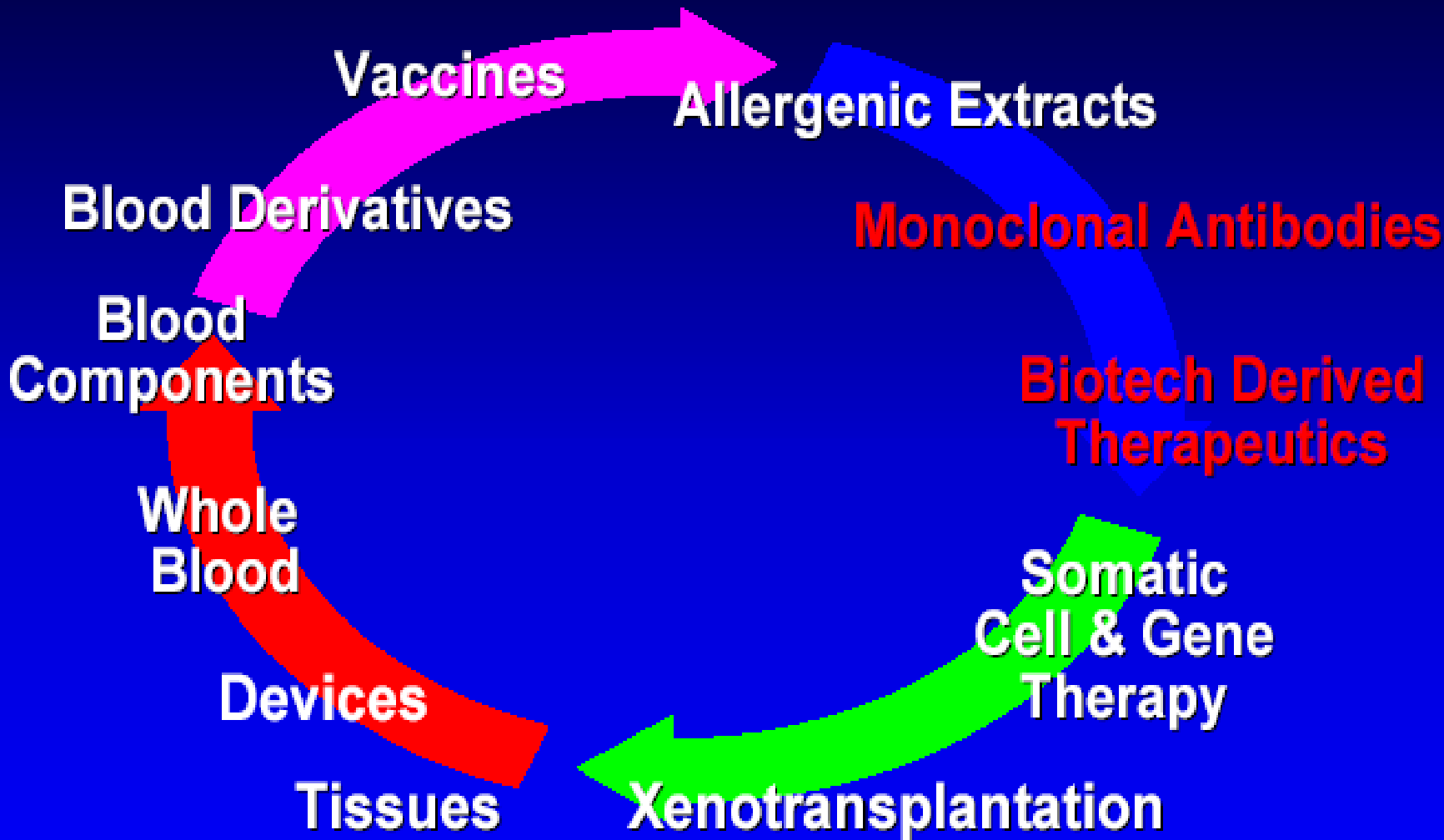
CBER → CDER

- History of biologics regulation
  - 1901 St. Louis tetanus tragedy -- Biologics Control Act (1902)
  - 1938 Food, Drug and Cosmetics Act incorporated 1902 to regulate biologics
    - NIH Division of Biologics Standards
  - Bureau of Biologics 1972 ~ 1982 – closer association with FDA
  - Center for Drugs and Biologics 1982 - 1987
  - Center for Biologics Evaluation and Research 1987-2002
  - September 6, 2002: CBER – CDER "Consolidation"

CBER – CDER "Consolidation"

- Forces for consolidation
  - 1990's – perceptions of increasing inconsistency, CBER: longer review times, multi-cycle reviews, poor communication
  - Consolidations options studies during '01
  - Principal Dep. Comm. Crawford's Q1 '02 review & outside consultants
  - 6/02 Imclone (Erbutux) hearing
  - 9/6/02 Crawford's FDA announcement
  - Implementation
    - Lumkin/Mullin lead implementation team
    - Phases
      - I – CDER/CBER distribution of products (Q4 '02)
      - II – Resources reallocation (Q1 '03)
      - III – Timeline / implementation ('03)

BIOLOGICAL PRODUCTS REGULATED BY CBER



What's Going

Monoclonal antibodies

Cytokines, growth factors, enzymes, interferons -- (including recombinant versions)

Proteins intended for therapeutic use that are extracted from animals or microorganisms (except clotting factors

Other therapeutic immunotherapies

What's Staying

- Monoclonal antibodies, cytokines, growth factors, or other proteins when used solely as an ex vivo constituent in a manufacturing process / when used solely as a reagent in the production of a product that is under the jurisdiction of CBER
- Viral-vectored gene insertions (i.e., "gene therapy")
- Products composed of human or animal cells or from physical parts of those cells

- Plasma expanders
- Allergen patch tests
- Allergenics
- Antitoxins, antivenins, and venoms
- In vitro diagnostics
- Vaccines
- Toxoids and toxins intended for immunization

Implications

- Consistency
- Meetings with industry
- Timeliness of reviews
- Transparency
- Concerns
  - Morale, reviewer retention
  - Current products in review
  - Scientific approach

Generic Biologicals

- **Generic Industry is eager & "prepared"**
- **USP is poised to set standards**
- **FDA is cautious, mostly silent**
  - **Comm. McClellan - GPhA 1/29/03: no mention of biologicals**
  - **FDA web search on "generic biologicals" = 0**
  - **CDER Dep Dir Galson's GPhA talk 10/15/02:** "Barriers"
    - Currently no statutory authority
    - How to demonstrate pharmaceutical equivalency bioequivalency ?
    - Duplication of manufacturing processes for biological products ?
    - Research on scientific standards - composition, formulation, equivalence
- **Congress is active**
  - **Sen. Hatch may introduce legislation to legalize generic biological drugs (BNA Pharmac. Law & Industry 1/24/03)**

Generic Biologicals

- **ABN-AMRO Special Report - Generic Biologics: The Next Frontier**
  - **With greater than $10 billion in brand sales of biologic products coming off patent over the next five years, and more to come in the years ahead, the opportunity for growth in this area is significant.**
    - **Generic biologics are in the foreseeable future**
    - **science has made it possible**
    - **Market potential has made it inevitable**
    - **Legislative initiative will make it feasible**
    - **Select number of companies have taken the initial steps towards capitalizing on this potential**
    - **Launches abroad (soon) will precede US launches**
    - **American public is keenly interested**

Selected Biotechnology Drugs Facing Patent Expiration

Brand Name (Generic Name)	Marketing Company	Indication	2000 Sales ($, millions)	U.S. Patent Expiry
Rebetron™ Combination Therapy (Ribavirin and Interferon alfa-2b)	Schering-Plough	Chronic Hepatitis C	1,361*	2001
Ceredase® (alglucerase)	Genzyme	Gaucher disease	537**	2001
Cerezyme® (imiglucerase)	Genzyme	Gaucher disease	537**	2001
Humulin® (human insulin)	Eli Lilly & Co.	Diabetes	1,137	2002
Novolin® (human insulin)	Novo Nordisk	Diabetes	260.4	2002
Intron® A (interferon alfa-2b)	Schering-Plough	Leukemia; Hepatitis B and C; melanoma; lymphoma	1,361*	2002
Avonex® (interferon beta-1a)	Biogen	Multiple Sclerosis	761	2003
Humatrope® (somatropin)	Eli Lilly & Co.	Growth hormone deficiency	303	2003
Nutropin®/Nutropin AQ® (somatropin)	Genetech	Growth hormone deficiency	226	2003
Epogen® (epoetin alpha)	Amgen	Anemia	2,034	2004
Procrit® (epoetin alpha)	Johnson & Johnson	Anemia	1,720	2004
Geref® (sermorelin)	Serono Laboratories	Growth hormone deficiency	0.045	2004
Synagis® (palivizumab)	Abbott	Respiratory syncytial viral	420	2005
Activase® (alteplase)	Genetech	Myocardial infarction, stroke, pulmonary embolism	206	2005
Protropin® (somatrem)	Genetech	Growth hormone deficiency	1.796	2005
Neupogen® (filgrastim)	Amgen	Neutropenia	1,224	2006
Albutein® (human albumin)	Enzon	Shock and hemodialysis	4.509	2006
Total			**10,197**	

* and ** Figure represents the combined sales for the two compounds.

Source: IMS Health, ABN AMRO estimates and FDA Orange Book

SOME FINAL OBSERVATIONS

- FDA clinical guidances are increasingly based on *principles of clinical pharmacology*
- "guidance" versus "regulation"
  - value added versus barrier
- FDA guidance
  - national "treasure" versus "national nuisance"
  - a bargain !
- Value of FDA guidance is related to the quality of sponsor data and preparation